REMARKS

Claims 1-5 and 8-14 are pending. The Examiner rejected claims 1-5 and 8-14. Applicants have herein amended claims 1, 10, 12, and 14, and cancelled claims 2-4. Amendments to the claims find support throughout the specification, e.g., at pages 2-3, 5-11, and Examples 1-6. No new matter has been added. Accordingly, claims 1, 5, and 8-14 are pending.

In light of the amendments and the remarks herein, Applicants respectfully request reconsideration and allowance of claims 1, 5, and 8-14.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 1-5 and 8-14 under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement. Citing the factors set forth in In re Wands, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988), the Examiner stated in particular that there was no support in the specification for the method; that the claimed results were directly opposite to the results of Kong *et al.* (WO 2001/61039) ("Kong"); and that "the problem of serotonin-based regulation of digestive tract responses is very complex." The Examiner went on to cite three references to support this assertion: Scherl *et al.* (Pharmacogenomics J., vol. 3:64-66 (2003)) ("Scherl"); Gershon (Rev. Gastroenterol. Dis., vol.3 (S2):S25-S34 (2003)) ("Gershon"); and Pata *et al.* (Am. J. Gastroenter., vol. 97:1780-1784 (2002)) ("Pata"). After reviewing the various references, the Examiner concluded that "in a highly unpredictable art where the antagonist-receptor effects in vivo depend on numerous known and unknown parameters, the factor of unpredictability weighs heavily in favor of undue experimentation."

Applicants respectfully disagree. With respect to the claims as amended, present claim 1 recites a method for predicting the responsiveness of a patient having diarrhea-IBS to alosetron. The method includes the steps of:

(a) determining a genotype of the promoter region of the patient's serotonin transporter protein gene, where the genotype is selected from the group consisting of a long variant/long variant, short variant/long variant, and short variant/short variant; and

(b) correlating the long variant/long variant genotype with a greater patient responsiveness to alosetron as compared to the responsiveness to alosetron of a patient having said short variant/long variant genotype or said short variant/short variant genotype.

Applicants respectfully assert that the present specification enables one skilled in the art to make and use the presently claimed invention. "To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1365 (Fed Cir. 1997). As acknowledged by the Examiner, the specification provides significant guidance as to how to determine the presence of the 5-HTTP gene promoter region polymorphism (see pages 5-6 and Example 3, page 13); how to correlate the genotype with diarrhea-predominant IBS patient responsiveness to alosetron using parameters such as colonic transit time (see pages 7-9 and Examples 2, 4, 5, and 6); how to treat patients with diarrhea-IBS having the long/long genotype with alosetron (see pages 9-10); and how to identify patients having diarrhea-IBS for clinical trials for alosetron (see pages 10-11 and the Examples).

Regarding the Examiner's assertions of unpredictability of the art based on the Kong results (i.e., wherein the short/short genotype was correlated with greater patient responsiveness to alosetron), Applicants point out that the Kong reference attempts to draw a correlation with genotype based on clinical response (e.g., patient subjective self-reporting of alleviation of symptoms; see Kong at page 21), rather than an objective pharmacodynamic endpoint (e.g., colonic transit time, as disclosed in the present application). Importantly, Applicants have demonstrated a statistically significant correlation between greater patient responsiveness to alosetron and the long/long genotype in the promoter region based on such an objective pharmacodynamic endpoint. See page 13 for a description of the statistical analyses used and pages 14-15 for a discussion of the results, including their statistical significance. Further, the proposed greater patient responsiveness of the short/short genotype in Kong is in direct contrast with the commonly-accepted mechanism of serotonin uptake in the synapse by the transporter

protein. As Kong notes on page 3, the deletion allele is associated with decreased gene expression of the transporter protein and decreased serotonin uptake. Decreased uptake by the transporter protein would result in increased serotonin in the synapse, thus rendering any serotonin receptor antagonist *less* effective (i.e., because of increased competition with serotonin for receptor binding). Thus, the presently claimed methods, and not the Kong methods, are based on the commonly-accepted mechanisms of serotonin uptake and regulation.

The Scherl, Gershon, and Pata references are similarly ineffective to demonstrate unpredictability of the presently claimed methods. As noted by the Examiner, Scherl characterized the results of the Camilleri study as "unable to correlate variability in SERT-P polymorphisms with gender-specific enhanced alosetron efficacy" and that "[f]uture studies evaluating the role of short polymorphisms of SERT-P in gender-specific clinical responses of D-IBS to 5HT3 antagonists are required." (emphasis added). Applicants respectfully point out that the presently claimed methods are not directed to correlating promoter genotype with gender-specific alosetron efficacy. As such, Applicants respectfully assert that the Scherl reference is an inappropriate reference to cite in support of the present enablement rejection.

The Gershon reference is similarly defective. After reviewing the Gershon reference, the Examiner concluded that the "interplay between the serotonin receptors and transporters is a very complex one, and the role played by either the serotinin transporter or 5-HT3 receptor in IBS is not clear." Applicants respectfully assert that whether or not the roles of the serotonin transporters or receptors in IBS are clear is not the appropriate standard for determining enablement of the presently claimed methods. Applicants refer the Examiner to the holding in Cross v. Iizuka, 753 F.2d 1040 (Fed. Cir. 1985), where the court noted that "[a]n inventor need not comprehend the scientific principles behind the invention. The inventor's theory or belief as to how his invention works is not a necessary element to satisfy the enablement requirement." As indicated previously, Applicants have provided significant guidance as to how to perform the full scope of the claimed methods; whether or not the roles of the serotonin transporter protein or receptor in IBS are clear is not relevant to that inquiry.

Finally, the Pata reference also fails to establish that the Applicants have not enabled the presently claimed methods. After reviewing the reference, the Examiner quoted Pata for the proposition that "[t]here are not enough studies attempting to determine the relationship between the SERT's gene functional capacity and receptor interaction and bowel functioning." The Examiner concluded that "the overall picture from the above publications is of uncertain correlation between the genotype of the SERT gene promoter region and IBS" . . . making it "difficult to determine with certainty that any single gene or receptor is responsible for IBS symptoms." (emphasis added). Applicants respectfully disagree. The present claims, moreover, are not directed to correlating the genotype of the SERT promoter with IBS or to determining that a single gene or receptor is responsible for IBS. Rather, the claims are directed to correlating the SERT promoter genotype with responsiveness of a patient having diarrhea-IBS to alosetron. As noted with the Gershon reference, Applicants are not required to determine the "single gene or receptor that is responsible for IBS symptoms" in order to enable the presently claimed methods. Instead, Applicants' burden is to enable the full scope of the claims, which Applicants have done, as indicated previously. Given the amount of guidance and detail in the specification as to how to perform the recited method steps, it would not require "undue experimentation" to perform the claimed methods. Accordingly, given all of the above, Applicants respectfully assert that the specification provides adequate teaching of the full scope of the present claims, and request the withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In light of the above amendments and remarks, Applicants respectfully request reconsideration and allowance of claims 1, 5, and 8-14. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Enclosed is a check for $55.00 for the one month extension of time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 5/7/04

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